Toxicity assessment for carcinogenic soil contaminants

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TOXICITY ASSESSMENT OF CARCINOGENIC SOIL CONTAMINANTS

NHMRC Technical Working Party on
Carcinogenic Risk Assessment for Soil Contaminants

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PREFACE

In 1992 the Australian and New Zealand Environment Conservation Council (ANZECC) and the National Health and Medical Research Council (NHMRC) developed guidelines for the assessment and management of contaminated sites. However, it was recognised at that time that further consideration was needed to develop a method for determining acceptable levels of carcinogenic soil contaminants (that is, those substances that could increase the number of certain types of cancer in people exposed to them). In 1995, the NHMRC established the Technical Working Party on Cancer Risk Assessment. This working party has proposed a method for assessment of cancer risk that is appropriate for contaminated sites in Australia. The method is described in detail in this report. This introductory chapter provides a brief summary of the key concepts behind the approach taken and the methods involved.

What is a contaminated site?

A contaminated site is a site where toxic chemicals that have the potential to be harmful to human health or to the environment are present at levels higher than those normally found in the area. This may occur following use of the land for industrial, agricultural or commercial activities. Contamination can also occur after waste disposal, spills or storage of raw materials, or from neighbouring properties following movement of the chemical (for example by wind, movement through the soil, or in ground or surface water). Chemicals that could be found at a contaminated site include metals (like lead or arsenic), oil, tar, explosive gases, solvents, or other poisonous or hazardous wastes.

Humans can be exposed to chemicals from a contaminated site in various ways. For example, by consuming contaminated water, by inhalation, by eating plants or animals that have been exposed, by skin contact from soil disturbance or, in the case of children, by ingesting soil from fingers, toys and other objects.

How do we know whether a contaminant poses a problem?

Deciding whether a site is a contaminated site, or whether the chemical contaminants at a particular site are of concern, involves a number of steps. The first step is to determine what chemicals are present, and at what concentrations. This can include looking at a site history, and may also include analysing samples from the site using sophisticated analytical methods.

The next step is to assess any problems that the chemicals identified can cause. This usually involves the evaluation of published experiments where the chemical has been deliberately given to experimental animals at high doses for a short time or at lower doses for a longer time. Other ways of identifying health problems include studying groups of people who have been accidentally exposed to the chemical, or looking for any health problems in workers who use the chemical. Once all the information has been evaluated, the process of describing the likely health problems that might arise from particular levels of the chemical can begin. This process is described later.

When a chemical has been found at a site and it has been determined that exposure to a certain level of the chemical may cause problems for human health, the next

step is to determine whether there is likely to be exposure of humans or the environment from the site in question. For example, a site that becomes part of a new housing development is more likely to cause exposure of people than one in a remote area. The environmental conditions at the site, such as the soil type, can also increase or decrease the chances of exposure.

Once the level of exposure that is likely to occur has been determined, calculations can be made of the likelihood and nature of health problems that could result from this level of exposure (toxicity assessment). The level of risk determined in this way affects how the site is managed.

What kinds of problems can these chemicals cause?

Chemical substances that are used in industry and agriculture have many benefits, but they can also cause a range of health problems, particularly at high doses. These can vary from minor problems, such as headaches or slight skin rashes, to major illnesses, including cancer. The effects of chemical contaminants vary depending on the chemical, the type of exposure, the amount to which a person is exposed (dose) and for how long. A serious effect that may be caused by some chemicals found at contaminated sites is an increase in the number of certain types of cancer in the people exposed.

What risk is acceptable?

The concept of 'acceptable' risk is very subjective and variable. There are no hard and fast rules or generally agreed principles on what level of risk is acceptable. Every day we all take decisions that involve a determination of the risks and benefits of particular activities. For example, driving a car poses a certain level of risk, while riding a bicycle or walking pose different levels of risk. The acceptable risk also changes when it is not your choice whether to be exposed or not (for example, the passive smoker who has to work or live with someone who smokes). How acceptable a risk is can also be influenced by many other factors, such as the seriousness of the problem caused and the cost of reducing the risk (eg cleaning up a site). For example, if a contaminated site is close to a residential community and is one where children play, people may be much less willing to accept risks than if the site is vacant and in an industrial area.

It is very difficult, and usually impossible, to determine the actual level of risk posed by very low levels of chemicals. Some people would prefer a zero level of risk, which they associate with zero levels of the chemical in the environment. While this is possible in theory, it is rarely possible in practice, particularly as our ability to detect chemicals improves so that we can detect extremely low levels of many chemicals.

How is cancer caused?

Cancer is a disease involving the abnormal growth of cells—affected cells grow and divide more than the cells around them producing a lump or tumour. It is not fully understood why cancer develops in some people and not in others. However, for all groups of people, a certain number will develop cancer at some stage of their lives. Studies in experimental animals have also shown that a certain level of cancer always occurs in animals that are allowed to grow and live normally. This is called

the background incidence of cancer. It has been recognised that exposure to some chemicals or other agents increases the rate of certain cancers above the background level. For example, exposure to sunlight increases the number of skin cancers, and cigarette smoking increases the number of lung cancers.

Although the exact way in which chemicals and other agents cause cancer is not fully understood, a common factor is that they all cause alterations to the genetic structure of cells. When the genetic structure is changed the cell may receive the wrong 'instructions' and begin to grow and divide to produce more cells like itself. Chemicals that cause this type of damage are called genotoxic carcinogens. However, it is now apparent that not all cancers are caused this way. In other cases, cells may receive the wrong instructions due to damage to other components of the cell. Chemicals that cause cancer without directly damaging the genetic material are called non-genotoxic carcinogens.

Because the development of cancer is such a complex process, the body's response to agents that cause cancer can be influenced by many factors, including diet, the health of the person at the time they are exposed to the chemical, and genetic differences between people in the way that chemicals are handled by the body.

How are the effects of chemicals assessed?

To assess the toxicity of a chemical, the first step is to gather together all the available information about the chemical. This may include studies using experimental animals that have been given a range of doses of the chemical for set periods; laboratory studies that try to show how the chemical acts on cells to change their genetic structure; and, if the chemical has been used widely, studies on workers or other people who have been exposed to the chemical.

For any type of cancer, there will be a background incidence of cancers in any species of experimental animals; some cancers are very rare, while others are very common in some types of animals. A dosing study therefore looks at how many more cancers are seen in animals that are treated with the chemical under investigation, than are seen in animals not exposed to the chemical.

To ensure that the animals within the groups are as alike as possible, careful breeding is used, and the conditions under which animals are kept is strictly managed. The largest number of animals practicable is used to increase the possibility that observed effects are not the result of chance. Equal numbers of males and females are used to allow any differences that occur because of the sex of the animal to be determined.

All of the information from the various studies is evaluated, including the quality of each study.

If it is clear from the animal studies that exposure to the chemical causes an increase in certain types of cancer in that species, a decision must then be made as to whether this indicates that a similar problem will occur for humans. Each species has differences in the way they deal with chemicals. In some cases a cancer is produced in a particular species because of the way they metabolise or break down a chemical. If humans don't metabolise the chemical in the same way, they may not be at risk of developing that kind of cancer.

It is sometimes also difficult to interpret human studies, such as those looking at workers who use the chemical or people who have been exposed to contaminated sites. This is because there are many possible causes for an increase in cancer in some individuals, including genetic differences, age, gender, diet, occupation and whether they smoked, and it is harder to control these factors or to take them into account than in animal studies.

If it is decided that the information shows that the chemical can produce an increase in cancer, and that this could occur in humans, then the next step is to calculate a level of the chemical that can be considered acceptable.

What is a 'safe' level of exposure?

All chemicals may be harmful under certain circumstances. Whether or not a particular chemical causes a toxic effect depends on a number of factors, including the type of chemical, the nature of the exposure, the dose and the susceptibility of the person or population exposed.

Safe doses have traditionally been determined based on the information available at the time about the development of cancer and other toxic effects. Because this information is limited, it has been necessary to make assumptions, or science policy decisions to determine safe, or acceptable, doses. Two different approaches have been used, based on different assumptions about the relationship between the dose of the chemical and the outcomes (dose–response relationship), particularly at very low doses. Different assumptions have been used for genotoxic carcinogens and for non-genotoxic carcinogens.

For most toxic chemicals, including non-genotoxic carcinogens, it has been assumed that a threshold dose can be determined below which no toxic or carcinogenic effects are seen (a non-linear response). Below this threshold dose, there may be too little of the chemical to cause damage. The body may be able to excrete the chemical (for example in the urine), change it to harmless derivatives before it causes any damage or repair any changes caused by the chemical.

For chemicals considered to have a threshold dose, a common approach to determining a safe dose has been to first determine a 'no observable adverse effect level' (NOAEL) from animal or human studies. This value is used as the starting point for calculation of an acceptable daily intake (ADI) or other measure of safety.

For genotoxic carcinogens, the assumption has been that no level of exposure is entirely safe (this is called a linear response and the equivalent of the NOAEL is zero dose). In this case it has been considered that even extremely low levels of the chemical may induce some damage to the genetic material and that this may be enough to increase the chance of developing a particular type of cancer. Larger doses will result in ever-increasing risk of cancer. In these cases, a method of determining a safe level has been used that involved determining the 'risk' of developing cancer at any dose greater than zero. This has been done by applying mathematical models to the experimental results in animals or humans to predict the increasing risk as the dose increases from zero. However, at extremely low doses accurate estimates of risk are very difficult to make.

Use of the threshold model for non-genotoxic carcinogens and the linear risk model for genotoxic chemicals has led to many difficulties as the way in which many chemicals cause cancer is not fully understood. Hence, different countries have applied these two approaches in different ways, even for the same chemical (eg dioxin). Because of this, values for 'safe' doses have been estimated that can vary considerably. In an extreme case, that of dioxins, the variation is more than 1000 times.

As more has been learned about the development of cancer, other toxic effects and biological mechanisms in general, the assumptions in these two approaches have been increasingly questioned. The Technical Working Party recognised these limitations and proposed that all carcinogenic chemicals should be assessed in the same way. They have developed a method that involves first determining a benchmark dose and then applying a number of safety factors, in order to obtain an acceptable safe dose. The benchmark dose is a dose that is related to a measurable or reliably predictable outcome (or benchmark) at a specified low level of increase above background levels. The safety factors are based on scientific assessment of all the available knowledge about a chemical and its effects. In this method, no assumptions need to be made about what may or may not happen at doses well below the levels that have actually been tested experimentally.

How is the benchmark dose determined?

Traditionally, the benchmark dose (BMD) has been determined for a specified risk using mathematical modelling from the dose–response relationship of a particular chemical (that is the changing incidence of the effects seen for differing doses of the chemical). This method has been developed and used quite widely overseas, mainly for risk assessment for non-cancer endpoints, but more recently also for cancer end-points. The traditional BMD that has been used for cancer is the upper dose of the 95 per cent statistical confidence interval producing a given increase level (usually in the range 1–10 per cent) in the incidence of cancers that occur above the background. The statistical confidence interval is a measure of the probability that the true value lies within an interval of values (in this case a 95 per cent probability that the dose that causes a specified increase in cancer above background levels lies within a dose interval bounded by the upper limit).

To obtain a more suitable measure for cancer endpoints, however, the Technical Working Party proposed a *modified*-BMD. They defined the *modified*-BMD as the dose of the chemical that produces a 5 per cent increase in the incidence of cancer above the background level based on the central estimate from the dose–response relationship, rather than on the upper 95 per cent statistical confidence limit. The central estimate is the dose that is 'most likely' to give this increase in cancer incidence.

If animals have only been dosed at high levels, deciding on a dose that is likely to produce a 5 per cent increase in cancer above background levels may require some mathematical prediction but it avoids many of the uncertainties of estimating extremely small increases in cancer at very low doses.

The *modified*-BMD from each relevant study is determined and each is subjected to further assessment to derive a 'guideline dose'. The method then involves the use of a range of safety factors that are applied to the each BMD to give a range of values for each effect. The lowest value is then chosen as the guideline dose. The guideline dose is considered to be a 'safe' dose that can form the basis for decisions on human exposure to the chemical.

How is the guideline dose determined?

A guideline dose is the average daily intake of a chemical which, over an average life time, should not result in cancer based on all the available information at the time of the assessment. It is calculated from the modified-BMD by applying four safety factors as follows:

- *Safety factor 1* – this factor accounts for possible differences between findings in experimental animals and humans (assuming the BMD was based on a study on experimental animals). If there is no information available on how similarly humans and the animal species used react to the particular chemical, this factor is ten and the BMD is divided by ten. If there is information indicating that people are either less or more sensitive to the chemical than animals then a factor of less or more than ten may be used.
- *Safety factor 2* – this factor accounts for variability within the human population in how people respond to chemicals. If there is no information on human variability for the particular chemical, the accepted default value is ten and the BMD is divided by ten.
- *Safety factor 3* – this factor accounts for the quality of the information. If the studies examined were very good and the assessors can be confident that the results are likely to be correct, this factor may be set at one. If the studies were not very good, however, it is possible for this factor to be as high as ten and the BMD is then divided by this factor.
- *Safety factor 4* – this factor accounts for how serious the cancer is and whether the chemical can cause genetic effects; the factor can reduce the benchmark dose by up to 50 times. To do this, the seriousness of the cancer is ranked on a scale from one to 50 based on three factors:
  - whether the cancer is malignant (a cancer that spreads throughout the body) or benign (a tumour that only grows in one place, and does not spread);
  - where the cancer occurs (some organs of the body, such as the skin, are not seriously affected by benign tumours while other organs, such as the brain or nervous system, are seriously affected by any abnormal growths, and even benign tumours which grow here are considered serious); and
  - whether the chemical can change the genetic material of cells. Changes to genetic material have been recognised as events that can start a cancer. Also, where a chemical can alter the genetic material of cells, a cancer could be started by a very small dose of the chemical.

Based on the above four safety factors, it is possible for the *modified*-BMD to be divided by up to 50 000 if the maximum safety factor is applied at each stage. This is equivalent to saying that you might see a 5 per cent increase in the incidence of a particular cancer if people drink 250 litres (or 25 buckets) of a particular chemical

per day (the benchmark dose). However, after applying the safety factors it might be considered that only 5 millilitres (or one teaspoon) is a safe level of exposure on a daily basis (the guideline dose). For most chemicals, based on the consideration described above, the overall safety factor applied would be somewhat smaller than this.

Once a guideline dose for cancer is calculated, it is compared with guideline doses calculated for other effects of the chemical. These could include other effects on body organs, such as changes in how the liver works or damage to kidney. The lowest dose is then chosen as the overall guideline dose for the chemical.

How will the guideline dose be used?

Once the guideline dose has been set, it can be used to determine whether the levels of the chemical concerned present at a contaminated site pose a human health problem, and can provide guidance for an appropriate management plan. The guideline dose is not intended to be used as a standard, or a fixed level indicating that action to reduce the level of a chemical is required, but as a guideline for decision making in particular situations.

To ensure that the information used and the reasons for the guideline dose are clearly understood, the Technical Working Party recommended that the assessors should produce a report for each substance assessed. The report should set out all the relevant evidence that has been used to arrive at the guideline dose, including uncertainties in the evidence. It should also explain the carcinogenic potential of the chemical in animals and humans and the conditions that lead to cancer developing.

How will the assessments occur?

The Technical Working Party recommended that an Expert Committee on Cancer Risk Assessment should be established with technical support and resources to implement the method described in this report. This should initially be for a few chemicals with differing properties to assess the applicability of the method and then for a priority list of chemicals to determine guideline doses for use in the assessment and management of contaminated sites.

In endorsing this document, NHMRC acknowledged that this is the first step towards developing a sound method for carcinogen risk assessment, the outcomes of which will be not only be protective of public health, but will be transparent, accountable and scientifically defensible. There will therefore be a need to monitor the application of the principles underpinning this approach and the performance of the method in the assessment and management of contaminated sites. NHMRC invites risk assessment practitioners to provide feedback on the application and outcomes of the methodology. Council will continue to review this document in light of the feedback and re-assess periodically the appropriateness of the methodology and its application in risk assessment processes.

ABBREVIATIONS

ADI	Acceptable Daily Intake (WHO)
ANZECC	Australia and New Zealand Environment and Conservation Council
ASCEPT	Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists
BMD	Benchmark Dose
BMD_L	Benchmark Dose Limit or Lower confidence limit on BMD
BMR	Benchmark Risk (Response)
DOH	Department of Health (United Kingdom)
DNA	Deoxyribonucleic acid
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
FDA	Food and Drug Administration (USA)
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LED	Lowest Effect Dose (US EPA, 1996)
LOAEL	Lowest Observed Adverse Effect Level
MTD	Maximum Tolerated Dose
NHMRC	National Health and Medical Research Council
NEPC	National Environment Protection Council
NEPM	National Environment Protection Measure
NOAEL	No Observed Adverse Effect Level
NTP	National Toxicology Program (USA)
PTWI	Provisional Tolerable Weekly Intake (WHO)
q_1^*	The 95 per cent confidence limit of the slope estimate used for the linear multi-stage model
RfD	Reference Dose (US EPA)
SAR	Structure Activity Relationship
TDI	Tolerable Daily Intake (WHO)
TWP	Technical Working Party
US EPA	United States Environmental Protection Agency
WHO	World Health Organization

EXECUTIVE SUMMARY

INTRODUCTION

1. During the development of the Australian and New Zealand Guidelines for the Assessment and Management of Contaminated Sites, the need for a method for dealing with carcinogenic soil contaminants was recognised. In July 1995, the National Health and Medical Research Council (NHMRC) established a Technical Working Party on Cancer Risk Assessment (the Technical Working Party; TWP) to examine the various methods and develop a method appropriate for contaminated sites in Australia. Whilst the Terms of Reference for the TWP require that it develop guidelines, the TWP considers it more appropriate to produce a technical guidance document *Toxicity Assessment for Carcinogenic Soil Contaminants* in the first instance, as it provides greater scope to explore the issues. This can be translated into a Guideline Document once the proposed method and recommendations of the TWP in this technical guidance are adopted.

2. The first draft of this document was produced in August 1996 and has undergone external, national and international peer review, consultation with major stakeholders from industry, government and the community through a series of seminars, and the statutory NHMRC public consultation process.

3. In performing its task the TWP has extensively reviewed and discussed existing methods which assess adverse health effects from exposures to environmental contaminants. Risk assessment methods used in the past can be categorised broadly into two groups based on two different assumptions about the shape of the dose-response curve and their putative mechanism of action: non-threshold and threshold. The distinction has been applied in particular to carcinogenic substances with and without genotoxic properties, respectively. In both cases, mathematical models are used to assess the risk of particular chemicals depending on their toxicological properties and mechanisms of action.

4. These methods have additionally been based on various conservative (default) assumptions in the absence scientific information. Following wide use, for a decade or more, many of their advantages and limitations have become apparent. The TWP has sought to develop a method for use in Australia which avoids some of the limitations inherent in existing cancer risk assessment methods. In particular, the use of all relevant scientific data in the decision-making process and the clear recognition and justification of the major components of the process: public health policy, professional judgement and scientific principles are fundamental to the proposed method.

5. This document presents a transparent and accountable method which uses the available scientific information about the toxicity of chemical agents while not requiring the assessor to make a judgement about the existence of a biological threshold, nor model mathematically the dose-response relationship below the range of experimental data to extrapolate at low environmental exposures. Scientific information is used to the maximum extent and thereafter policy considerations and professional judgements are made clear and explicit. Rationale and recommended defaults for proceeding through the analysis are explained.

6. Practitioners conducting site specific toxicity assessment using these guidelines and method would be required to demonstrate levels of technical expertise commensurate with their (recognised) qualifications.

7. Rapidly advancing molecular technologies are providing the tools that permit a more detailed understanding of the carcinogenic process and are providing mechanistically based approaches for testing chemicals. While this type of data is currently limited, the proposed method sets the stage for future incorporation of this important information into the assessment of environmental carcinogens.

8. The results of an assessment using this method will not necessarily yield a human exposure dose which differs greatly from those derived by currently used methods. However, the method provides the opportunity to establish a Guideline Dose which may be less overtly conservative when new, acceptable data are available regarding mechanisms of action, toxicokinetics and toxicodynamics.

DECISION PROCESS FOR CONDUCTING TOXICITY ASSESSMENT OF CARCINOGENIC SOIL CONTAMINANTS

9. The contaminated site assessment model described by the ANZECC/NHMRC (1992) consists of four major facets: data collection and evaluation, toxicity assessment (some refer to this step as chemical risk assessment, or hazard assessment and dose-response assessment), the exposure assessment and the contaminated site risk characterisation. This guidance document addresses the second of these facets: the toxicity assessment (collecting the information on and assessing the hazard and dose-response of chemical carcinogenic agents). The data collection and evaluation (about the site contamination), exposure assessment and site risk assessment, as well as procedures for assessing non-carcinogenic chemicals are presented elsewhere (see ANZECC/NHMRC, 1992).

10. The end result of the carcinogen risk assessment process for a particular chemical is a Guideline Dose which is the average daily intake of a chemical which, for a life time, should not result in cancer, based on the information available at the time of the assessment.

11. The Guideline Dose may be used in the development of health investigation levels, response levels and risk characterisation of human exposures to contaminants in soil. Although produced by the TWP to fulfil the terms of reference given by the NHMRC to address soil contaminants, this method is a comprehensive approach which may be applied to contaminants in any media. This approach is consistent with international risk assessment methods.

12. The process begins with assembling all relevant, peer-reviewed scientific literature and other scientifically sound data. These data are assessed for their scientific quality and adequacy, and also evaluated for their applicability in the *modified*-Benchmark Dose (*modified*-BMD) method. Guidance is provided in Appendix A.

13. Next follows a judgement of whether the carcinogenic responses observed in the chosen studies are causally associated with exposure to the given agent. That is, does the chemical agent pose a carcinogenic hazard? Guidance for evaluating epidemiological and *in vivo, in vitro* and other experimental evidence is provided in Appendix B.

14. If the agent is considered to pose a carcinogenic hazard, the assessor(s) must determine whether the observed hazard(s) are relevant to humans. This is particularly important where only animal data are available or human data are limited. Guidance is provided in Appendix C.

15. For carcinogenic hazards relevant to humans, a *modified*-BMD approach is applied to each suitable experimental data set and the *modified*-BMD corresponding to the 5 per cent and 1 per cent extra risk of each experimental data set is determined. The *modified*-BMD corresponding to the 5 per cent extra risk in the animal bioassay or human study is used as the starting point for deriving the Guideline Dose. The *modified*-BMD corresponding to the 1 per cent extra risk is determined to assess the volatility of the models outside the experimental range. Guidance is provided in Appendices D and E.

16. Guideline Doses are obtained by applying factors to each *modified*-BMD. Derivation of the factors involves four primary decision points:

    (i) Assessment and evaluation of the data relating to differences between experimental animals and humans;

    (ii) Assessment and evaluation of the data relating to individual variability within the human population;

    (iii) Assessment and evaluation of the quality of the data available; and

    (iv) Assessment and evaluation of the seriousness of the cancer response.

    Guidance is provided in Appendix F. The Guideline Dose chosen for further derivation of guidance values should be the lowest dose as well as be supported by the highest possible strength and weight of evidence.

17. Uniquely, the proposed method assigns factors in a range of 1–50 for the seriousness of the carcinogenic response. Derivation of these factors involves three decision points:

(i) Are tumours malignant?

(ii) Are tumours in a critical organ?

(iii) Does the agent pose a genotoxic hazard?

Appendix F provides the explanation of these factors.

18. The lowest Guideline Dose for the carcinogenic hazard is compared with tolerable intakes derived for non-cancer endpoints (eg the Acceptable Daily Intake, ADI) and the lower value of the Guideline Dose or the other tolerable intake is used for risk characterisation and further guideline development in the human health risk assessment as described by ANZECC/NHMRC (1992).

19. The assessment process leading to the Guideline Dose is documented in a transparent way in an assessment report. This report should include: a discussion of the strength and weight of evidence, uncertainties in the data, limitations in the interpretation, any assumptions made, including whether or not they are default assumptions, qualitative assessment of exceeding the Guideline Dose, and guidance for any further research needed. Guidance for preparing the report is provided in Appendix G.

MAJOR SCIENCE POLICY DECISIONS/RECOMMENDATIONS

20. The TWP proposes a risk assessment method in which no assumptions are made about the shape of the dose-response curve substantially outside the experimental range. The *modified*-BMD provides a reproducible, consistent starting point for derivation of Guideline Doses for carcinogens whether or not they possess genotoxic properties.

21. The *modified*-BMD is derived from the point estimate of the dose associated with the central estimate of the 5 per cent extra risk. This contrasts with the traditional Benchmark Dose (traditional BMD) which is associated with the 95 per cent upper statistical limit associated with the chosen response rate.

22. The benefits of the proposed approach include:

- it is applicable to all carcinogens, genotoxic or non-genotoxic;
- it takes into account all dose-response information;
- it uses all available, relevant information; and
- it uses a more data sensitive endpoint, ie the point estimate of the central tendency, for identifying the dose associated with 5 per cent extra risk.

23. Although the proposed *modified*-BMD approach for toxicity assessment overcomes many of the limitations of other methods, it does not dispense with, nor account for some of the other uncertainties inherent in biological data or mathematical modelling. Consequently, due care should be taken to describe the uncertainties.

24. The TWP considers that the Guideline Dose for carcinogens is protective of public health. However, the Guideline Dose for carcinogens should not be perceived as a dose which, if exceeded, results in an adverse human health response in all cases. The Guideline Dose report will contain a qualitative assessment based on the strength and weight of evidence of the likely consequences of exceeding the Guideline Dose.

25. This method does not address toxicity assessment for mixtures of individual chemicals, nor physical, radiological or biological entities. However, acceptable, relevant dose-response data for a characterised mixture may be used in the described method.

26. Flow charts and breakdown components of factors with specific numerical ranges as shown in Appendix F are provided to increase overall understanding of the method's conceptual basis and to aid the practitioner in applying the method. They are not to be interpreted as rigid rules.

27. For many years, it has been recognised that default assumptions are necessarily made in risk assessments where gaps exist in general knowledge or in the available data for a particular agent. These default assumptions are inferences based on general scientific knowledge as well as matters of policy on appropriate ways to bridge uncertainties about the potential risks to human health from the agent under assessment (US EPA, 1996). In the proposed method, the evaluator is guided toward decisions based on the scientific data base. Recommendations on default assumptions are provided for cases where the data are incomplete to bridge data gaps and allow the risk assessment to proceed. All choices, both those based on scientific data and those based on default assumptions, must be supported by reasoned and critical analytical arguments.

28. All available studies deemed adequate should be considered when making a judgement on whether or not the chemical poses a carcinogenic hazard. Limited studies can contribute to the judgement as far as their deficiencies permit.

29. The presence of a dose-response relationship is most important in judging the significance of an increase in tumour incidence. Any apparent dose-related increase in the incidence of a neoplasm should be scrutinised rigorously and appropriate statistical analyses applied. In most cases, statistical analyses would have been conducted by the authors of the study/report, in which case the analyses should be assessed for adequacy.

30. The decision of whether or not a chemical poses a carcinogenic hazard to humans will be made based on all available information, eg on the strength and weight of evidence. In the absence of human carcinogenicity studies, the TWP considers that, following a decision that a chemical is carcinogenic in animals, the default assumption is that it poses a carcinogenic hazard to humans.

31. The TWP recognises that, when available, the best scientific choice to describe the dose-response relationship would be a biologically-based mechanistic model. When an appropriate model is not available, the TWP recommends that, for the sake of consistency and ease of use, the Quantal Weibull, Logit (or Probit) and linear models are applied to the data. For each carcinogenic response considered relevant, it is recommended that the average of the three central estimates of the dose associated with a 5 per cent extra risk be derived using these models. This average (or averages, in the case where there are more then one relevant carcinogenic response) is the starting point for the application of the factors to derive the Guideline Dose for each relevant carcinogenic response.

32. To derive a human equivalent dose from animal data, the preferred option is to use toxicokinetic data which provide biologically equivalent doses. Physiologically-based, pharmacokinetic modelling or other models may provide useful information. In the absence of validated modelling, the default procedure is to scale the daily applied dose in proportion to body weight and apply a factor to account for interspecies differences. The size of the factor will depend on the data available (See Appendices E and F).

33. In the proposed risk assessment method, genotoxic aspects of a carcinogen are addressed by the application of separate factors, based on a reasoned assessment of the genotoxic hazard which considers all available data in studies judged to be acceptable. In the absence of data to the contrary, it is reasonable to infer that a genotoxic animal carcinogen poses a genotoxic carcinogenic hazard to humans.

34. Factors for interspecies variability, intraspecies variability, quality of the data base and seriousness of the carcinogenic response are derived according to a decision tree which takes into account all of the available data; hence, using scientific judgement to address a number of the uncertainties in the risk assessment process. The value of the overall factor may range up to 50 000. In cases where the overall factor is less than 50 or greater than 25 000, the data base should be re-examined to determine whether or not the data are suitable for assessing human carcinogenic hazard of the agent.

35. The risk assessment narrative is a comprehensive characterisation presenting the strength and weight of evidence, and describing the likelihood that the agent poses a carcinogenic hazard to humans. The description should summarise all relevant biological evidence and reflect the uncertainties in the evidence and the complexity of carcinogenesis and its assessment process. It should explain the carcinogenic potential in animals and humans and the conditions of its expression.

36. The TWP recommends that an Expert Committee on Cancer Risk Assessment be established with adequate technical support and financial resources to implement the method described in this guidance document. The Expert Committee on Cancer Risk Assessment should consist of at least two toxicologists, one epidemiologist, and one statistician with experience in

mathematical modelling. These experts as well as others with experience in risk assessment, biochemistry, molecular biology, pathology and other relevant specialties can be drawn from a pool of specialists as required. The Committee would meet on an ad hoc basis and would probably conduct most of its business out-of-session.

37. As its first task, the Expert Committee on Cancer Risk Assessment should address the following issues: the influence of background incidence in the dose-response, that is, the use of concurrent and/or historical controls; development of a priority list of chemical agents; recommendations for dose-response data which should be modelled for genotoxic agents lacking bioassay studies; recommendations for an approach for the assessment of indirect genotoxins; recommendations regarding use of *in vitro* testing methods to address the hazard and dose-response of chemical mixtures and recommendations regarding modelling epidemiological data to determine a *modified*-BMD.

38. The TWP recommends that the method be tested on a limited number of chemicals with differing toxicological properties to assess its application for determining Guideline Doses for substances of concern in the assessment and management of contaminated sites. Following this, the method should be applied to the priority list of chemicals to derive Guideline Doses for use in the assessment and management of carcinogenic soil contaminants. These are beyond the scope of the brief of, and the time frame allocated to, the TWP.

39. To facilitate the use of models and computation of the mean *modified*-BMD, the TWP also recommends that a suitable computer program be developed to automate the derivation of *modified*-BMD by fitting the three models to the experimental data.

40. Should the method outlined in this technical guidance document and the recommendations of the TWP be adopted and guidelines for cancer risk assessment be developed from this guidance document, the TWP recommends that the guidelines should include a number of worked examples to illustrate the application of the method.

41. This document and its method should not be interpreted or applied as rules or standards for assessing toxicity. The document does not provide a mandatory framework and the method does not provide a regulatory value. Rather it seeks to establish a balance between prescription and scientific judgement, using a toxicity assessment process which allows for data appraisal by an expert committee. In assessing toxicity using this method, such a committee may then make regulatory recommendations to Government. It is the intention of the guidance document to effect a toxicity assessment process that is quantifiably transparent and to enhance the method's validity and value.

42. In endorsing this document, NHMRC acknowledged that this is the first step towards developing a sound method for carcinogen risk assessment, the outcomes of which will be not only be protective of public health, but will be transparent, accountable and scientifically defensible. There will therefore be a need to monitor the application of the principles underpinning this approach and the performance of the method in the assessment and management of contaminated sites. NHMRC invites risk assessment practitioners to provide feedback on the application and outcomes of the methodology. Council will continue to review this document in light of the feedback and re-assess periodically the appropriateness of the methodology and its application in risk assessment processes.